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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/315,292	05/20/1999	CLARENCE FRANK BENNETT	ISIS-3561	6344
55389	7590	10/22/2010		
KNOBBE, MARTENS, OLSON & BEAR, LLP 2040 MAIN STREET FOURTEENTH FLOOR IRVINE, CA 92614			EXAMINER BOWMAN, AMY HUDSON	
			ART UNIT 1635	PAPER NUMBER
			NOTIFICATION DATE 10/22/2010	DELIVERY MODE ELECTRONIC

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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<b>Office Action Summary</b>	<b>Application No.</b>	<b>Applicant(s)</b>	
	09/315,292	BENNETT ET AL.	
	<b>Examiner</b>	<b>Art Unit</b>	
	AMY BOWMAN	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

#### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) ☒ Responsive to communication(s) filed on 09 September 2010.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) ☒ Claim(s) 99, 100, 103-107, 109, 110, 113-117, 119, 121 and 128 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 99, 100, 103-107, 109, 110, 113-117, 119, 121, and 128 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 20 May 1999 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \*    c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

- |   |   |
|---|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)                    | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____                                      |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)         | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____   | 6) <input type="checkbox"/> Other: _____                          |

### **DETAILED ACTION**

Applicant's response filed 9/9/10 has been considered. Rejections and/or objections not reiterated from the previous office action mailed 3/9/10 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action

Claims 99, 100, 103-107, 109, 110, 113-117, 119, 121, and 128 are pending in the instant application.

### ***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 99, 100, 103-107, 109, 110, 113-117, 119, 121, and 128 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nyce et al. (WO 96/40266) (cited and of record on PTO-892 mailed on 5/10/06), in view of Nicklin et al. (WO 98/09633) (cited and of record on PTO-892 mailed on 5/10/06) and Levesque et al. (Molecular Pharmacology, 51, 1997, pages 209-216) (cited and of record on the PTO-892 mailed on 5/1/08).

Nyce et al. teach that antisense oligonucleotides may be administered to the lungs of a patient by any suitable means, but preferably administered by generating an aerosol comprised of respirable particles, the respirable particles comprised of the antisense compound, which particles the subject inhales (see page 10).

Nyce et al. teach that respirable antisense oligonucleotides can be formulated to be liquid or solid (see page 10). Liquid compositions comprise the antisense compound and sterile, pyrogen free water or saline solution (see page 9, for example). Nyce et al. teach that suitable formulations for delivery include powders (see page 12). Nyce et al.

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teach that respirable antisense oligonucleotides can be formulated into powders and effectively delivered with a metered dose inhaler. Nyce et al. teach methylphosphonate and phosphorothioate linkages to render respirable antisense oligonucleotides more stable *in vivo* (see page 7).

Nyce et al. teach that particles comprised of antisense compound should be of respirable size that is particles of a size sufficiently small to pass through the mouth and larynx upon inhalation and into the bronchi and alveoli of the lungs. Nyce et al. teach that in general, particles ranging from about .5 to 10 microns in size are respirable (see page 10). Therefore, Nyce et al. teach respirable particles “about 1 to about 5 microns”, as instantly recited. Nyce et al. teach that the antisense oligonucleotides may be of any suitable length, e.g. from about 10 to 60 nucleotides in length (see page 8) and specifically exemplify an 18-mer and a 21-mer (see pages 14 and 15) that is phosphorothioated.

Nyce et al. teach a method of administering the aerosolized antisense oligonucleotides to animals *in vivo* (see page 16, for example) and teach uptake of the oligonucleotide in the lungs. Nyce et al. teach methods of treating asthma via administering an antisense oligonucleotide to the lung of a subject (see page 3).

Nyce et al. teach that the dosage of the antisense compound administered will depend upon the disease to be treated, the condition of the subject, the particular formulation, the route of administration, the timing of administration to the subject, etc. Nyce et al. teaches that a dosage of from about .01, .1, or 1 mg/Kg up to 50, 100, or

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150 mg/Kg or more is typically employed to treat a human (see page 11). Nyce et al. teach nebulizers and formation of aerosols for delivery of the compound (see page 12).

Nyce et al. do not teach 2'-O-methoxyethyl or 5-methylcytosine modifications.

Nicklin et al. teach antisense oligonucleotides and teach that modification of antisense oligonucleotides confers increased nuclease resistance, increased uptake into cells, and increased binding affinity for the RNA target (see page 2). Nicklin et al. teach 2' modifications including 2'-alkoxyalkoxy, 2'-O-methoxyethyl, and 2'-O-dialkylaminoalkoxy modifications (see pages 2-4). Nicklin et al. teach phosphorothioate, methylphosphonate, and non-phosphorous containing linkage modifications (see pages 4 and 5). Nicklin et al. teach that in certain especially preferred embodiments, all backbone linkages are phosphorothioate linkages. Nicklin et al. teach that preferred bases include at least one 5-methylcytosine. Nicklin et al. teach chimeric configurations having one or more regions of 2'-modified nucleotides, particularly 2'-methoxyethoxy nucleotides (see page 4). Nicklin et al. teach antisense oligonucleotides that are 20 nucleotides in length (see pages 5-10, for example).

Levesque et al. teach that a 20-mer phosphorothioate antisense oligonucleotide which contains 2'-methoxyethyl modifications reduced target mRNA expression, wherein the mismatched control had no effect (see summary, page 209).

It would have been obvious to incorporate 2'-O-methoxyethyl modifications, as taught by Nicklin et al. and Levesque et al. and 5-methylcytosine modifications, as taught by Nicklin et al. into the antisense oligonucleotides taught by Nyce et al.

One would have been motivated to incorporate 2'-O-methoxyethyl or 5-methylcytosine modifications into the oligonucleotides of the method of Nyce et al. because Nicklin et al. teach that such modifications confer increased nuclease resistance, increased uptake into cells, and increased binding affinity for the RNA target. Furthermore, Levesque et al. teach that a 20-mer phosphorothioate antisense oligonucleotide which contains 2'-methoxyethyl modifications reduced target mRNA expression, wherein the mismatched control had no effect. Since Nyce et al. teach other modifications, such as incorporation of phosphorothioates, in order to render the respirable antisense oligonucleotides more stable *in vivo*, one would have been motivated to incorporate other modifications as well that were also known in the art to enhance oligonucleotide activity, as evidenced by Nicklin et al. and Levesque et al.

With regards to the level/degree of modification, as well as the specific dosage, it would have been prima facie obvious to perform routine optimization to determine the optimal level of modification as well as the optimal dosage, as noted in *In re Aller*, 105 USPQ 233 at 235,

More particularly, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.

Routine optimization is not considered inventive and no evidence has been presented that the particular range used was other than routine, that the products resulting from the optimization have any unexpected properties, or that the results should be considered unexpected in any way as compared to the closest prior art. It was known in the art to deliver modified antisense compounds via aerosol delivery, each of the

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modifications were known to enhance the delivery of antisense compounds, and the instant doses are within the dosing ranges set forth by Nyce, wherein Nyce teaches the considerations of dosing for optimization.

The instant claims require various broad quantities of each type of modification. It was known in the art at the time the invention was made to deliver oligonucleotides to the lung of mammals via introducing aerosolized oligonucleotides of the instantly recited size range and particle size range that are modified, as taught by Nyce et al. The only difference between the instantly recited method and the method of Nyce et al. is the specific types of chemical modifications, wherein each of the instantly recited chemical modifications were known in the art to benefit the stability of antisense oligonucleotides, as evidenced by Nyce et al., Levesque et al., and Nicklin et al. It is within the realm of routine optimization to incorporate various quantities of the known chemical modifications, as it was known in the art to incorporate the chemical modifications into chimeric configurations, as evidenced by Nicklin et al. Additionally, Levesque et al. specifically teaches successful target inhibition when utilizing a 20-mer antisense oligonucleotide with phosphorothioates and 2'-methoxyethyls. Therefore, it would have been obvious to try to the instantly recited combination of modifications at different levels/quantities in view of the teachings of Nicklin et al., Levesque et al. and Nyce et al.

Finally, one would have a reasonable expectation of success that the chemical modifications taught by Nicklin et al. and Levesque et al. would benefit the antisense oligonucleotides of Nyce et al. because each of the instantly recited modifications were



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known in the art at the time the invention was made to enhance the activity of antisense oligonucleotides, as evidenced by Nicklin et al., Levesque et al. and Nyce et al.

Thus in the absence of evidence to the contrary, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

### ***Response to Arguments***

Applicant argues that the examiner's position that each of the instant chemical modifications was known in the art to benefit the stability of antisense oligonucleotides and to enhance delivery is not supported by the evidence of record. Applicant asserts that the only evidence of record is the declaration by Dr. Richard Geary, wherein the opinion declaration sets forth that he does not interpret the Nicklin et al. reference as supporting that the incorporation of 2'-O-methoxyethyl modifications would result in an increased uptake of a nucleic acid to the cells.

The basis of applicant's arguments regarding the evidence of record is unclear given that Nyce et al. teach methylphosphonate and phosphorothioate linkages to render respirable antisense oligonucleotides more stable *in vivo* (see page 7); and Nicklin et al. teach antisense oligonucleotides and teach that modification of antisense oligonucleotides confers increased nuclease resistance, increased uptake into cells, and increased binding affinity for the RNA target (see page 2). Nicklin et al. teach 2' modifications including 2'-alkoxyalkoxy, 2'-O-methoxyethyl, and 2'-O-dialkylaminoalkoxy modifications (see pages 2-4). Nicklin et al. teach

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phosphorothioate, methylphosphonate, and non-phosphorous containing linkage modifications (see pages 4 and 5). Nicklin et al. teach that in certain especially preferred embodiments, all backbone linkages are phosphorothioate linkages. Nicklin et al. teach that preferred bases include at least one 5-methylcytosine. Nicklin et al. teach chimeric configurations having one or more regions of 2'-modified nucleotides, particularly 2'-methoxyethoxy nucleotides (see page 4). Nicklin et al. teach antisense oligonucleotides that are 20 nucleotides in length (see pages 5-10, for example).

Furthermore, Levesque et al. teach that a 20-mer phosphorothioate antisense oligonucleotide which contains 2'-methoxyethyl modifications reduced target mRNA expression, wherein the mismatched control had no effect (see summary, page 209).

Applicant is reminded that this is a rejection under 35 USC 103(a), rather than under 35 USC 102 and therefore it is the combination of the references that renders the instant claims obvious. Given that it was known that aerosolized antisense oligonucleotides can be successfully delivered with resultant uptake of the oligonucleotide in the lungs, wherein the oligonucleotide has a modification for the purpose of increasing stability, as taught by Nyce et al., it would have certainly have been obvious to incorporate other chemical modifications that are utilized with antisense oligonucleotides for the same purpose of enhancing delivery, such as the modifications taught by Nicklin et al. and Levesque et al. Given that Nyce et al. teaches aerosol delivery, Nicklin et al. teaches 2'-O-methoxyethyl and 5-methylcytosines, as well as teaches the purpose of modifications is to confer increased nuclease resistance, increased uptake into cells, and increased binding affinity for the RNA target, and

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Levesque et al. teach that a 20-mer phosphorothioate antisense oligonucleotide which contains 2'-methoxyethyl modifications reduced target mRNA expression, wherein the mismatched control had no effect, there is certainly motivation to incorporate these modifications with a reasonable expectation of success. Furthermore, there would be a reasonable expectation that conferring increased nuclease resistance, increased uptake into cells, increased binding affinity for the RNA target, and/or increased stability would in fact result in an increase of uptake compared to those oligonucleotides without the modification.

Although applicant argues that the level/degree of modification is not a matter of routine optimization, the instant claims are not directed to any specific static pattern of modification, but rather encompass a large genus of possible modification patterns. For example, the oligonucleotide has at least one phosphorothioate, at least one 2'-O-methoxyethyl, and every cytosine is a 5-methylcytosine. Therefore, the modification pattern embraces a huge genus of possible combinations of quantities of phosphorothioate and 2'-O-methoxyethyl modifications, varying from one of each minimum to every position of each maximum, and every possible combination in between, combined with 5-methylcytosine modification that varies in quantity and position depending upon the target sequence.

Therefore, it is the instant genus that is considered obvious in view of the teachings of the prior art, given that the prior art teaches the benefits of each of the instant modifications, teaches different combinations of the instant modifications, and teaches to deliver oligonucleotides to the lung of mammals via introducing aerosolized

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oligonucleotides of the instantly recited size range and particle size range that are modified, as taught by Nyce et al. The only difference between the instantly recited method and the method of Nyce et al. is the specific types of chemical modifications, wherein each of the instantly recited chemical modifications were known in the art to benefit the stability of antisense oligonucleotides, as evidenced by Nyce et al., Levesque et al., and Nicklin et al.

It is within the realm of routine optimization to incorporate various quantities of the known chemical modifications, as it was known in the art to incorporate the chemical modifications into chimeric configurations, as evidenced by Nicklin et al. Additionally, Levesque et al. specifically teaches successful target inhibition when utilizing a 20-mer antisense oligonucleotide with phosphorothioates and 2'-methoxyethyls. Therefore, it would have been obvious to try to the instantly recited combination of modifications at different levels/quantities in view of the teachings of Nicklin et al., Levesque et al. and Nyce et al.

Applicant asserts that the instantly claimed method provides unexpected results and compares ISIS 15163 and ISIS 17009 to support such an assertion. There is no reason to expect that combining the modifications that are taught to enhance stability (and wherein Nicklin teaches that chemical modifications enhance uptake) would not result in some level of uptake when incorporated into the method of Nyce. If applicant questions that the combination of these modifications would result in uptake, enablement of the instant claims is in question.

Therefore, it is not unexpected for oligonucleotides with the instant combination of modifications to result in uptake. In order to demonstrate that such a property is unexpected, applicant would need to point to some teaching that sets forth that this combination would likely not result in uptake, which clearly is not the case given that the art teaches the benefits of each of the instant modifications. One would certainly have been motivated to combine the modifications of the prior antisense art and would expect some level within the instant genus as a re

Furthermore, the specific oligonucleotides that applicant points to for unexpected results are not commensurate in scope with the instant claims. The example pointed to by applicant is comparing one specific oligonucleotide sequence (therefore does not consider different levels of cytosine modification based upon target sequence), wherein ISIS 15163 has (6) a phosphodiester backbone, 5-methylcytosine modifications based upon the example target sequence, and is modified with 2'-O-methoxyethyls; and ISIS 17009 is phosphorothioated. The instant claims require a combination of all three of these types of modifications and thus the example pointed to by applicant is not representative of the instant genus. Applicant is relying upon one example within a huge genus of molecules, wherein even the single example is not representative of the instantly claimed oligonucleotide within the instant method.

With regards to the teaching of Nicklin regarding increased uptake into cells, Nicklin is clearly referring to the modifications taught by Nicklin. Furthermore, there is no reason to expect that the combinations of modifications taught by Nicklin would not

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result in cellular uptake given the benefits taught by Nicklin in incorporating such modifications.

Regarding the opinion declaration by Dr. Richard Geary, the declaration does not set forth any reason why one would not expect for the combinations of modifications to result in cellular uptake, which is the instantly recited intended outcome. The declaration does not set forth any reasoning why combining the modifications of the prior art for the benefits set forth by the prior art would not result in uptake into cells, particularly given that Nyce teaches aerosol administration of modified oligonucleotides and therefore the instant rejection is only based upon incorporating the instant types of modifications. There is clearly motivation in the prior art to combine modifications, including the instant types of chemical modifications, wherein clearly the desire is to reach a target cell via the combination of chemical modification and aerosol delivery.

### ***New Rejections***

#### ***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 99, 100, 103-107, 109, 110, 113-117, 119, and 121 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the

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inventor(s), at the time the application was filed, had possession of the claimed invention. THIS IS A NEW MATTER REJECTION.

Applicant points to example 3 for support for the instant claim amendments. However, upon a review of the specification and particularly at example 3, support is not evident for oligonucleotides 8 to 30 nucleotides in length having at least one 2'-O-methoxyethyl modification in combination with each cytosine being a 5-methylcytosine with a resultant enhancement in the amount taken up by the lung in comparison to a control of the same sequence.

Example 3 demonstrates such an outcome with regards to a specific 2'-O-methoxyethyl 20-mer, wherein the oligonucleotide comprises 6 C nucleotides at specific positions that are 5-methylcytosine modified. This is not representative of the instantly claimed genus of molecules having the instantly recited outcome.

Claim 100, for example, requires a phosphorothioate modification, which is not an element of the 2'-O-methoxyethyl modified oligonucleotide of example, but is rather an element of the control sequence that was less effective at uptake.

Furthermore, support is not evident in the instant specification for at least one phosphorothioate linkage as recited in claims 100 and 110.

MPEP §2163.06 notes:

If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement. In re Rasmussen, 650 F.2d 1212, 211 USPQ 323 (CCPA 1981).

MPEP §2163.02 teaches that:

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Whenever the issue arises, the fundamental factual inquiry is whether a claim defines an invention that is clearly conveyed to those skilled in the art at the time the application was filed...If a claim is amended to include subject matter, limitations, or terminology not present in the application as filed, involving a departure from, addition to, or deletion from the disclosure of the application as filed, the examiner should conclude that the claimed subject matter is not described in that application.

A review of the specification does not reveal support for where the claim amendments are found. Should applicant disagree, applicants are encouraged to point out with particularity by page and line number where such support might exist for each claim limitation added in the amended claims filed on 9/9/10.

There is no support for this claim limitation in the claimed priority documents. Therefore, the effective filing date of the instant claims is considered, for purposes of prior art, to be 5/20/99, which is the filing date of the instant application.

### ***Conclusion***

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to AMY BOWMAN whose telephone number is (571)272-0755. The examiner can normally be reached on Monday-Thursday 6:00 - 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on (571) 272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.



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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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